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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/368,989 | 08/05/99 | STEVENS | F 0003/00332 |

HM22/0424
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EXAMINER

COOK, L

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1641

DATE MAILED: 04/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/368,989

Applicant(s)

STEVENS ET AL.

Examiner

Lisa V. Cook

Art Unit

1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 February 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10-14 and 21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-14 and 21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____

DETAILED ACTION

1. Applicants' response to the Office Action mailed August 30, 2000 (Paper #7, filed 2/01/01) is acknowledged. In amendment-A filed therein claims 1-9 and 15-20 were cancelled without prejudice, claims 10 and 12 were amended, and new claim 21 was added. Please not applicants' erroneously numbered the new claim 15 however, claim 15 has been cancelled at applicants request. Therefore the new claim should be number 21. Currently, Group II (claims 10-14 and new claim 21) are pending and under consideration. Claims 10-14 were rejected under 35 U.S.C.112 second paragraph, 35 U.S.C. 101, 35 U.S.C. 102(a)(b), and under 35 U.S.C. 103(a).

OBJECTIONS WITHDRAWN

Oath/Declaration

2. A new oath or declaration is required because the second inventor (Schiffer) did not provide date of signature. The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02.

The newly submitted Declaration executed and dated by inventor Schiffer has obviated this objection.

Specification

3. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

4. The disclosure is objected to because of the following informalities: The attempt to incorporate subject matter into this application by reference to web sites <http://www.rcsb.org/pdb/> and <http://www.sdsc.edu/> is improper because Applicants have embedded a hyperlink which is impermissible and requires deletion. (see page 10 of the disclosure). This attempt to incorporate subject matter into the patent by reference is improper because PTO policy does not permit the PTO to link to any commercial sites since the PTO exercises no control over those organizations, views or accuracy of the information contained on those outside sites. All web sites were deleted from the specification by amendment, the objection is withdrawn.

OBJECTIONS MAINTAINED

Drawings

5. The drawings in this application are objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner. Applicant has deferred response to this objection.

Information Disclosure Statement

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on form PTO-1449 lists the references, they have not been considered. Applicant has not addressed the objection, it is maintained.

REJECTIONS WITHDRAWN

Claim Rejections - 35 USC § 112

7. Claims 10-14 and new claim 21 are withdrawn from rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record on paper number 5. Applicants' amendments and arguments have obviated the rejections set forth in paper #5.

Claim Rejections - 35 USC § 102 and 35 USC § 103

8. Claims 10 – 13 are withdrawn from rejected under 35 U.S.C. 102(b) as being anticipated by Hoogenboom et al. (WO 93/06213). Claims 10 – 13 are withdrawn from rejected under 35 U.S.C. 102(b) as being anticipated by Stevens et al. (Protein Science, 1995, Vol.4, pages 421-432). Claim 14 is withdrawn from rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens et al. (Protein Science, 1995, Vol.4, pages 421-432) or Hoogenboom et al. (WO 93/06213) in view of Goling (Journal of Immunology, 1980, 124(5), pages 2082-2088)-Abstract Only and Skoog et al. (Scand. J. Immunology, 1980, 11(4), pages 369-376)-Abstract Only.

Applicants' amendment and arguments directed to the molecule comprising a first moiety and second moiety derived from the same gene being engineered to be juxtaposed to each other were fully considered and found persuasive. Therefore the rejections under 35 USC 102 and 35 USC 103 of record in paper #5 are withdrawn.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 10-14 and 21 remain directed to non-statutory subject matter. The inventions as claimed read on any molecule, where the molecule includes products of nature. Non-naturally occurring compositions are considered to be patentable subject matter within the scope of 35 U.S.C. 101. Compositions that are products of nature are considered non-statutory and non-patentable. See Official Gazette, 1077 O.G. 24, April 21, 1987. It is recommended that the claims incorporate the claim language, "isolated" or "purified" to overcome this rejection. Although the claims have been modified to recite a purified first moiety and a purified second moiety, the preamble recites a molecule. It is suggested that the preamble recite "a synthetic molecule or a purified/isolated molecule" to obviate this rejection.

NEW GROUNDS OF REJECTION NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 10-14 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Independent claim 10 now recites a limitation wherein the antigen binding domains and the antigen non-binding domains are contiguous with each other. See specification page 4, lines 4-8 for example. This limitation is not supported by the disclosure. The disclosure merely teaches an antigen binding region and an antigen non-binding region with out any particulars with respect to the regions being in contact with each other. Applicant is invited to point out support for this limitation in the disclosure.

11. Claims 10-14 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for constructs having complementary determining segments (CDRs) positioned at opposite ends of a dimeric assembly, does not reasonably provide enablement for all unnatural configurations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims as written read on any and all unnatural configurations producing constructs. However, the specification fails to provide any teaching or guidance with regard to the generation of any unnatural configuration, other than

constructs having complementary determining segments (CDRs) positioned at opposite ends of a dimeric assembly – specification page 7, lines 13-25. The art of recombinant molecule generation is not a predictable art with respect to unnatural configuration production.

Without evidence to the contrary, unnatural configurations producing any molecules according to the instant claims is not predictable and would vary according to the type of unnatural configuration imposed on the molecule at varying sites of the molecule. Given such a wide range of possible site manipulations and the vast number of diverse molecules that could be produced, one of ordinary skill in the art would have been required to undergo undue experimentation to determine which configuration would produce the desired molecule.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 10 – 13 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Pokkuluri et al. (Structure, 15 August 1998, 6, pp1067-1073).

Pokkuluri et al. disclose the same methods of producing bivalent molecules capable of binding two moieties as the instant claims. This statement is supported by the disclosure on page 8, lines 4-8 wherein Pokkuluri et al. are sited to teach detailed procedures of domain flips in immunoglobulin molecule subunits in order to place two identical binding sites at opposite poles of dimer constructs.

In one embodiment a polypeptide comprising a heavy or light chain variable domain of a non-human antibody specific for an antigen of interest. The structure of the LenQ38E dimer was discussed in detail. Further, in this reference structural reshaping of the beta-sheets or molecular remodeling was successfully accomplished.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102((e), f) or (g) prior art under 35 U.S.C. 103(a).

I. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pokkuluri et al. (Structure, 15 August 1998, 6, pp1067-1073) in view of Goling (Journal of Immunology, 1980, 124(5), pages 2082-2088)-Abstract Only and Skoog et al. (Scand. J. Immunolgy, 1980, 11(4), pages 369-376)-Abstract Only.

Please see Pokkuluri et al. as set forth above.

Pokkuluri et al. differ from the instant invention in not specifically reciting the weight requirements of claim 14. (between 20,000 and 30,000 daltons).

However, both references of Goling and Skoog et al. teach that the protein structure in the range of 20,000 to 30,000 daltons is important in surface receptor, immunoglobulin activity.

Hoogenboom et al., Stevens et al., Goling, and Skoog et al. are analogous art, because all four references teach methods concerning proteins.

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to utilize a molecule weighing between 20,000 and 30,000 daltons as taught by Goling and Skoog et al. in the method/product of Pokkuluri et al. to produce a dimeric antigen binding molecule.

A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such compounds, because such weight ranges were previous demonstrated. One of ordinary skill in the art would have been motivated to do this because Goding taught that protease cleavage of the lymphocyte surface IgD typically resulted in one light chain disulfide bond fragment weighting 30,000 daltons. Skoog et al. further taught that SDS polyacrylamide gel electrophoresis exhibited a broad peak at the molecular weight range of 20,000-35,000 daltons for surface receptors.

Response to Arguments

14. Applicant's argument with respect to constructs having multiple binding sites, derived from the same gene source, and engineered via unnatural configuration has been fully considered but is not found persuasive in light of the new rejection set forth above. Because all of the limitations are taught in the reference of Pokkuluri et al.

15. For reasons aforementioned and already of record, no claims are allowed.

Remarks

16. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure: Both references disclose general procedures relative to multivalent molecule production in order to increase stability and specificity.

A. Pluckthun et al (Immunotechnology 3, 1997, 83-105)

B. Raag et al. (FASEB, J, 9, 1/1995, pages 73-80)

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Art Unit: 1641

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Lisa V. Cook

Patent Examiner

Art Unit: 1641

CM1 7B17

703-305-0808



**LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600**

04/21/01